Modern Concepts of Cardiovascular Disease

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MEDICAL MANAGEMENT OF ARTERIAL OCCLUSION AND THROMBOPHLEBITIS

ACUTE ARTERIAL OCCLUSION

The list of causes of arterial occlusion is a very long one, but most examples are accounted for by thrombosis over an arteriosclerotic plaque, embolization from a fibrillating or infarcted heart or thrombosis from the inflammation of thromboangiitis obliterans. The diagnostic signs of a limb with acute arterial occlusion are extreme pallor on elevation, cyanosis at a horizontal level in the early stages, coolness of the affected area, absent or greatly diminished peripheral arterial pulses and oscillometric readings. Pain and numbness are usually present. The oscillometer is especially valuable in indicating the level at which the obstruction exists. Pulses occluded or diminished by vasospasm may be released of this spasm by sublingual glyceryl trinitrate given as a diagnostic test (1).

Management

1. Direct Surgery

In the case of a sudden embolization, if expert vascular surgery is available, less than 8 hours have transpired and the general condition of the patient will tolerate it, embolectomy is the treatment of choice if the obstruction is at the bifurcation of the aorta, the iliac artery or femoral artery down to the popiiteal area. Popliteal emboli and those distal to it do better without surgery. It is now considered wise to recommend anticoagulant therapy during the post-operative course.

2. The Use of Gravity

To aid the flow of blood down collateral channels the affected limb must be kept below heart level. This may be accomplished by elevating the head of the bed on blocks. The common error of raising the involved limb on a pillow is to be deplored. Alternately filling the limb with blood by making it dependent and then draining it by elevating it slightly can be conveniently accomplished by the oscillating bed of which several types are available. The bed must be regulated to suit each case. The aim should be to obtain just enough elevation on the upswing to drain the veins but not maintained long enough to produce marked pallor. The down swing should give ample gravity-pressure flow to produce rubor if possible without reaching an angle uncomfortable to the patient.

3. Vasodilatation

Collateral vessels are very sensitive to environmental changes both chemical and physical. Slight chilling can cause extreme vasoconstriction. Proper warmth produces dilatation of the arterial tree.

(a) *Avoidance of Tobacco*

The use of tobacco in any form produces profound vasoconstriction. Some patients are much more sensitive to this than others. Even a single puff of a cigarette may cause measurable vasospasm. Complete abstinence from tobacco is a "sine qua non" for successful therapy. In addition to acting as a vasoconstricting agent, in thromboangiitis obliterans there is evidence to show that the acute inflammation, which is the characteristic pathogenic feature of the disease, may be due to a peculiar idiosyncracy to tobacco.

(b) *Warmth*

Heat should never be applied to an area with decreased arterial flow. However, when the area proximal to it is warmed, a reflex vasodilatation may follow. For example, if the popliteal artery is occluded, a heating pad may be placed on the abdomen or groin.

(c) *Drugs*

1. *Intraarterial*
   The injection of a direct acting medication into an artery above the point of obstruction may be helpful. Histamine infusion by the technique of Mufson (2) or priscoline given slowly by syringe act directly on the arterial wall and may be helpful in overcoming an acute occlusion with marked spasm. Care must be exercised to traumatize the artery as little as possible.
2. *Systemic*
   The use of general vasodilators (alcohol, nicotinic acid derivatives) and ganglion blocking agents (hexamethonium compounds, priscoline, tetraethyl ammonium halides), and dibenzaline have their limitations. Their use is controversial at this time. In our hands sublingual glyceryl trinitrate in a dose of 0.0004 gm. has given the maximum degree of dilatation of large and small arteries for periods of 1 to 2 hours. Except in cases of occlusion by spasm of the major arteries one should not expect a warming of skin by this drug.

(d) *Nerve Blocks*

The most effective method for releasing vasospasm in the legs is the injection of procaine into the lumbar sympathetic ganglia. It is a very useful procedure and frequently is effective for periods up to 8 hours. The results are not as generally effective when this technique is applied to the upper extremities. Deep injections such as these must not be given if the patient is receiving anticoagulants because of danger of hemorrhage.

(e) *Sympathectomy*

Rarely, sympathectomy may be resorted to in acute occlusion. It has the effect of a long lasting sympathetic block but the disadvantage of subjecting an often severely ill patient to a major procedure.

(f) *Induced Fever*

General vasodilatation occurs in fever. This may be induced by intravenous injection of typhoid vaccine. An initial dose of 5 million organisms is used, increasing by 3 to 5 million organisms with each dose. The aim is to produce a slight fever without a chill. This form of therapy is most helpful in cases of thromboangiitis obliterans with marked vasospasm.

4. Maintenance of Tissue Viability

While the limb with major arterial insufficiency is awaiting the development of collateral flow, the tissues in jeopardy must be protected against maceration, infection, dehydration and thermal damage. It is unwise to speed up their metabolic rate by the application of external heat. The increased oxygen need cannot be met and the tissues die. On the other hand, cooling is apt to produce vasoconstriction and decreased blood flow. In general, the affected limb should be kept in an environment of 70° to 88° F. Wet compresses are contraindicated because of their tendency toward cooling and the heat loss by evaporation further chills the part. Gently coating the limb with an inert fat and then wrapping it loosely with cotton wool will help maintain an ideal environment and protect against maceration.

Cold or ice are only applied when it has been decided to amputate. When so used they relieve pain, reduce absorption from an infected area, and allow time for the patient to be satisfactorily prepared for the operation.

5. Anticoagulants

In patients with embolization as, for example, from a heart in auricular fibrillation, anticoagulants are particularly useful in preventing further emboli. They also aid in prevention of extension of thromboses. During the period of greatly reduced blood flow in the affected limb, thrombosis "in situ" in the capillary bed and small vessels, together with thromboses in the veins, is a constantly feared phenomenon. Adequate anticoagulant administration will help combat this tendency.

6. General Measures

Supportive measures should not be overlooked in the focusing of attention on the threatened limb. Problems associated with serious underlying disease such as polycythemia, old rheumatic heart disease, myocardial infarction or diabetes mellitus should be appropriately treated.

CHRONIC ARTERIAL INSUFFICIENCY

If the limb survives the acute occlusion, a chronic state of arterial insufficiency often follows. Closure of an artery may also be very gradual. The patient may have then developed intermittent claudication, necrotic ulcers or gangrene.

Management

Many of the principles outlined above are applicable with some modification to the treatment of chronic arterial insufficiency.

1. The Use of Gravity

The patient should sleep with the head of his bed elevated or, if possible, use an oscillating bed.

2. Vasodilatation

(a) *Avoidance of Tobacco* (see above)
(b) *Warmth*

In addition to reflex heat mentioned above, if open lesions are not present, the ambulant patient may take warm Sitz baths daily with the water at 98° F. for 30 minutes.

3. Drugs

If the skin lesions are present, vasodilators which shunt the blood to the skin circulation may be of value. Alcoholic beverages are probably as effective as other means and well accepted by people of middle age and beyond. Priscoline, since it is quite active orally, is the preferred ganglion blocking agent for those who can tolerate it.

4. Sympathectomy

The value of sympathectomy in the chronic stage is controversial. It gives best results in patients with increased vasomotor tone who have skin ulcerations. Increased blood flow to the muscles should not be expected from the operation. In patients with normal or decreased vasomotor tone, it may result in a decreased total blood flow to the affected limb. We reserve sympathectomy for patients who have not done well on the conservative regimen outlined above, including the absolute prohibition of tobacco. In general, the results in such cases are not striking; in fact, they are frequently very disappointing.

5. Care of Ulcers

Necrotic ulcers must be cared for with great gentleness. Debridement should be done minutely and at many sittings. Amputation of necrotic toes often leaves a necrotic, non-healing stump. Hot soaks must be strictly avoided for reasons given above. The temperature of saline soaks used daily should be from 90 to 95° F. Wet dressings are too cooling. Strong chemicals only add to the necrosis. Mild antimicrobial ointments with a wide spectrum are best. Furacin soluble dressing is excellent if the physician is alert to skin sensitization.

6. General Hygiene

The patient must avoid chilling. In cold weather he should wear heavy underwear and stadium boots. He should be cautioned never to put heat in any form (including diathermy) on the involved limb (see #4 under acute occlusion). He must not take vasoconstrictor drugs such as epinephrine, ephedrine, benzedrine or ergot derivatives. He should always keep the affected limb below heart level. If he has intermittent claudication he should keep his walking at a slow rate below the point of pain. If pain occurs he should stop until it disappears.

The outlook for patients with chronic arterial occlusive disease is much better than commonly accepted by the medical profession, provided that they are persistent in their adherence to the regimen outlined above. This may mean a matter of years rather than weeks and the patient must be oriented regarding the long range approach to his problem at an early visit.

THROMBOPHLEBITIS

Inflammation in or around a vein with clot formation is known as thrombophlebitis. When intravascular thrombus formation is due to venous stasis or to alterations in the blood which increase the clotting tendency and is only followed secondarily by inflammation, it is frequently termed phlebothrombosis. It is often difficult to classify a case as belonging clearly into either group. While in some patients the process at the time of onset is of one or the other type, after several days inflammation and thrombosis are usually coexistent.

Classification and Etiology

The classification presented here is from the Nomenclature of Diseases of the Blood and Lymph Vessels prepared by a committee of the American Heart Association.

1. Thrombophlebitis and venous thrombosis (phlebothrombosis)
   - (a) Primary
     - (1) Thromboangiitis obliterans
     - (2) Recurrent or migrating (without arterial lesions)
     - (3) Essential
   - (b) Secondary to
     - (1) Mechanical injury (contusion, laceration, surgery)
     - (2) Muscular effort or strain
     - (3) Chemical injury (sclerosing agents, drugs, solutions for diagnosis)
     - (4) Inflammatory or suppurative lesions—infectious diseases
       - (a) Tuberculosis, syphilis, actinomycosis
       - (b) Other bacteria (to be specified)
     - (5) Infectious diseases
     - (6) Severe ischemia
     - (7) Chronic disease of vein wall (varices, phlebosclerosis). (Later complications —varicose or postphlebitic ulcers)

(8) Blood dyscrasias (polycythemia vera, leukemia, pernicious anemia)
(9) Congestive heart failure
(10) Caricinoma

2. Neoplastic invasion of vein
3. Venous compression—with or without thrombosis of thrombophlebitis due to:
   (a) Gravid uterus
   (b) Neoplasm
   (c) Aneurysm
   (d) Scar tissue
   (e) Scalenus syndrome
   (f) Fractures and dislocations
   (g) Increased intra-abdominal pressure (ascites, etc.)
   (h) Extrinsic pressure (tight girdles, circular garters, poorly made trusses, etc.)

The wide variations in etiology and mechanism are clear in the above classification. The underlying factors in any one case may be further simplified. Trauma or damage to a vein wall may initiate a thrombus formation especially when a substance to be injected is irritating in nature, such as arsenicals, ascorbic acid, glucose, aureomycin and certain of the opaque media used for x-ray visualization of the vascular tree. In addition, it is now established that cortisone, ACTH and certain oral arsenical compounds should be used with great caution in the presence of any condition which exhibits a thrombotic tendency. It is recommended that crystalline trypsin not be used in clinical practice pending further studies regarding its thrombotic as well as fibrinolytic action. Stasis per se may be the inciting factor. Increased tendency to clot formation in itself may lead to thrombosis as in cases of pancreatic neoplasm.

Diagnosis

The finding of a red, tender, hot, painful cord in the course of a vein is the pathognomonic sign. Frequently, however, a deep vein is involved without superficial signs. In such cases, reliance is placed on indirect findings to make a diagnosis. These are dependent edema and cyanosis of the affected limb, the dilatation of collateral veins, deep muscle tenderness, pain on passive motion or stretching, fever, and constitutional symptoms. Often edema and swelling may be masked and revealed only by accurate limb measurements (circumference), comparing equal levels in opposite extremities.

Treatment

1. Elevation

An involved extremity should be elevated approximately 6 in. above the level of the heart. This is especially indicated in the presence of edema. The purpose is to facilitate drainage of static lymph and venous fluid from the extremity. The measure adds greatly to the patient's comfort. Elevation is best accomplished by raising the foot of the bed 8 in. on blocks. The use of pillows alone too frequently results in elevation of the knee above the foot and therefore interferes with proper drainage distal to the knee. In the presence of occlusive arterial disease, it is unwise to elevate the extremity. The use of an oscillating bed will help to reduce the edema safely. Otherwise the extremity should be kept in a horizontal position.

2. Rest

Although it is important to keep the patient active as a preventive postoperative measure in order to discourage the production of clots and the development of thrombophlebitis, once thrombophlebitis has been recognized the patient should be placed at bed rest.

3. Heat

Gentle warmth is one of the best means of releasing venospasm and producing analgesia. Arteriospasm is also a frequent complication of phlebitis. A warm moist pack gives relaxation of both arterial and venous trees comparable to that produced by lumbar ganglionic block, may be maintained over long periods, and is a great deal simpler. The packs are at first applied for 20 out of each 24 hours, decreasing the time as the condition improves.

4. Nerve Blocks

Rarely it may be necessary to perform sympathetic nerve blocks to release vasospasm. It is considered hazardous to perform this procedure while active anticoagulant therapy is in progress.

5. Analgesia and Treatment of Cramps

Night cramps may frequently be relieved by 0.2 gm. of quinine sulfate at bedtime or by 0.05 gm. of benadryl.

6. Antifungus Therapy

Dermatophytosis of the toes because it is a portal of entry for microorganisms should be actively combated by the usual means ($KMnO_4$ foot soaks 1/10,000, Whitfield's ointment or undecylic acid ointments.)

7. Constitutional Treatment

Dehydration must be avoided particularly since it increases the tendency to thrombus formation Unless there is some cause of sodium retention (e.g. renal or cardiac disease) edema will not increase from a liberal fluid intake.

8. Anticoagulant Therapy

The use of anticoagulants requires well trained teams of workers and laboratories prepared to provide meticulous service. Unless the laboratory's technique for determination of the prothrombin time is properly standardized and can be depended on, use of coumarin derivatives or Phenylindanedione should not be attempted. When home therapy is undertaken, provision should be made for frequent determination of the prothrombin level by reliable laborary technicians.

Barker et al. (3) at the Mayo Clinic have clearly demonstrated the great value of dicumarol in prevention of pulmonary emboli in treating cases of phlebitis. Zilliacus (4) and other Swedish workers have shown a similar beneficial effect with heparin. These results have been reproduced in many clinics throughout the world.

The experimental work of Burt and his colleagues (5) indicates that clots are absorbed more quickly if the patient receives anticoagulant therapy.

Technique of Administration of Anticoagulants

(1) The prothrombin time is determined by the Quick or Link-Shapiro technique before the first dose is given. Normal readings are 12-13 seconds by the Quick method and 13-17 seconds by the Link-Shapiro method.

(2) If the prothrombin time is normal or lower, 300 mg. of Dicumarol is administered orally in one dose. If emboli have occurred, Heparin may be started immediately and continued until the Dicumarol effect is manifested.

(3) Each day the prothrombin time is determined and reported to the physician in charge of the case before the Dicumarol dosage for that day is decided on.

(4) Dicumarol is administered in doses of 200 mg. daily until the prothrombin time is 30 seconds, and in doses of 25 to 100 mg. (depending on the patient's sensitivity to the drug) daily when the prothrombin time is between 30 and 35 seconds on the ascending portion of the curve.

(5) When the prothrombin time reaches 35 seconds, Dicumarol is discontinued until the prothrombin time drops below 30 seconds, after which it is given again cautiously in daily doses of 25 to 200 mg. (The foregoing prothrombin time values were determined by the Link-Shapiro method.) Frequently the time rises for several days after Dicumarol is discontinued and then returns toward normal.

(6) If the prothrombin time reaches 60 or 70

seconds, hemorrhagic manifestations may occur, and one must be alert to the possibility. At a level of 60-65 seconds 64 to 72 mg. of synthetic, water soluble vitamin K (or 500 mg. of vitamin K_1 orally) should be given parenterally and repeated in 4 hours. On our service, hemorrhagic manifestations have been very rarely observed as purpuric spots, minor oozing from the gums and some red blood cells in the urine. If encountered, more severe hemorrhagic manifestations may usually be checked by one or two transfusions of 300-500 cc. of whole fresh blood (may be citrated) or by giving vitamin K_1 orally. The objective is to keep the prothrombin level between 30 and 35 seconds, especially during the first two or three weeks. The dosage is then tapered off slowly, permitting the time to drop below 30 seconds, followed by a gradual return to normal. Dicumarol has been continued in most of our cases until the patient has resumed his accustomed activities. This is usually from 15 to 30 days after the last episode of thrombosis or embolism.

When embolic phenomena have already occurred it is sometimes advisable to give Heparin during the first 24 to 48 hours until the effect of the first dose of Dicumarol is established. Continuous drip still appears to be the theoretical method of choice although it is difficult to regulate and tedious on the patient. In practice, few hospital staffs can continue the regimen required for many days without some break in the technique.. The clotting time must be checked every two hours day and night by the Lee-White method. The optimal time should be maintained at twice normal to insure effectiveness without danger of hemorrhage.

Intermittent parenteral injections of Heparin cause wide fluctuations in clotting time. This method, giving 50-75 mg.* intravenously every four hours, is widely used in Sweden and has been favorably reported on by Jorpes, Bauer, Zilliacus and others. The clotting time rises rapidly to 60 to 70 minutes and falls normal before the next dose is given. This would appear risky and unphysiologic, but the Swedish workers have demonstrated that, practically, it is sound. For seven years now we have used this method extensively, with satisfactory results and without complications. The use of a vehicle causing slow absorption would be helpful, but to date those proposed have been disappointing. Pitkin's menstruum, including the recent modifications, causes wide fluctuations and difficulty in control and its use has been so painful that many patients prefer continuous infusion. It may also cause nausea. Depoheparin (Upjohn) is less painful and somewhat more satisfactory to use but is still unpredictable. We use the following dose schedule: 200 to 300 mg. for the first dose and 200 mg. on an average of every 12 hours if the clotting time is not in excess of twice normal just before the next dose. If it is in excess of this, the dose should be delayed accordingly.

Sublingual administration of Heparin has failed completely to produce any change in the clotting time in tests run in our laboratory.

Tromexan

Tromexan, which is also a coumarin derivative closely related to Dicumarol, on the average acts more quickly and on discontinuation ceases to act more quickly than Dicumarol. With Tromexan, the first dose is 1,500 mg. (1,800 mg. if the patient is obese). The second day the prothrombin time is usually prolonged. If it is not above 35 seconds, the patient is given 300 mg. three times (total 900 mg.). Thereafter the usual dosage is 300 mg. two or three times a day depending on the prothrombin time.

*The international standard used in the United States is 160 per cent as strong as that used in Sweden; hence our dosage is apparently lower than the 75 to 125 mg. recommended by the Swedish workers.

Phenylindanedione

Phenylindanedione has been used as an anticoagulant. It is not a coumarin, but it does reduce the prothrombin activity and thus prolongs the prothrombin time. The most satisfactory initial dose ranges from 300 to 400 mg.; further doses are adjusted according to the prothrombin time tests. The action of P.I.D. or Danilone, as it is called, resembles that of Tromexan more than of Dicumarol.

Cyclocumarol, (4-Hydroxycoumarin No. 63), (BL 5), (Cumopyran)

This drug acts at about the rate of Dicumarol, but its action is much more prolonged so that doses need be administered only at two to five day intervals. The average maintenance dose is 125 to 150 mg. and should be regulated by the prothrombin time tests.

After Care

During the acute phase of thrombophlebitis, the valves of the involved veins often become enmeshed in the inflammatory action, and deformed or destroyed. During the course of time the absence of these valves manifests itself in the involved leg by the signs of chronic venous insufficiency. These signs develop slowly over the course of months and years. They are: varicose vein formation, congestion of dependent tissues, especially at the ankle, hemosiderin deposit, plexus formation, stasis dermatitis, and ulceration of the skin.

To prevent this unfortunate chain of events, the following instructions are given to the patient when he leaves the hospital or assumes his normal mode of living:

(a) Elevation—the patient should sleep with the foot of the bed elevated on blocks 6 to 8 inches high.

(b) Compression—when up and about, he should wear a firm, well-fitted elastic stocking extending from just above the toes to one inch below the knee.

(c) Hydrotherapy—swimming or walking in deep water should be encouraged.

In other words, every effort should be made to prevent the edema from becoming static or fixed until the compensating venous circulation is able to develop.

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